1. Background

In 1982, the Federation of American Societies for Experimental Biology (FASEB) initiated the sponsorship of Summer Research Conferences fashioned after the already established Gordon Research Conferences. This conference format required that approximately 100 participants devote four and half days to the review and discussion of a selected topic of research. Since then, a number of conferences encompassing a broad range of topics have taken place at two sites, namely in Vermont and Colorado. In 1991, FASEB sponsored the first Summer Conference on 'Chromatin and Transcription'. This was held at Copper Mountain, Colorado with Gordon Hager (NCI) as Chairman and Michael Grunstein (UCLA) as Vice Chairman. In addition, a group of established scientists in this area were selected to chair the individual sessions. As the interests of the Chairman and Vice Chairman were focussed on biochemical and genetic approaches to chromatin function, both of these areas were well represented in the final program.

As the first Summer Conference on Chromatin and Transcription, the 1991 meeting generated a great deal of interest and was regarded as a major success. Universal enthusiasm was expressed for the continuation of the meeting both in terms of format and focussed content. Alan Wolffe (NIH) whose work concerns biochemical approaches to chromatin function was selected as Chairman of the 1993 FASEB Conference on Chromatin and Transcription. Dan Gottschling (University of Chicago), whose previous research has focussed on genetic approaches to chromatin function in yeast was selected as Vice-Chairman, thus maintaining equal representation of biochemical and genetic approaches to this important problem.

2. Justification and Aims

The current proposal is designed to stimulate focussed interaction between scientists exploiting predominantly genetic and biochemical approaches to understand how nuclear architecture impacts on the transcriptional regulation of genes. Rigorous experimental proof has emerged from several American and European laboratories that the transcriptional regulatory regions of many genes are organized into precise nucleoprotein structures including transcription factors, histones and in some cases RNA polymerase. This structural organization modulates gene activity in ways distinct from that directed by transcription factors alone. Genetic approaches using yeast and Drosophila have strengthened this inter-relationship between chromatin structure and transcription. Thus there is a compelling need for investigators with diverse skills and experimental approaches involving expertise in the basal transcriptional machinery, chromatin assembly and structure, developmental biology, and Drosophila and yeast genetics to meet and formulate concepts and approaches to this problem of how chromatin structure impacts on transcription.

Progress in a number of research areas documents the rapid development of this field. Several gene systems in yeast and larger eukaryotes have been characterized both in terms of nucleoprotein structure in vivo and the contributions of the relevant transcription factors. Transcription factors have been found to directly influence nucleosome positions. Such interactions and those directed by DNA sequence alone have facilitated the experimental manipulation of nucleosome position and assessment of the important functional consequences.

These in vivo experiments have been extended in vitro using systems that correctly assemble and space nucleosomes. The functional consequences of staged nucleosome/chromatin assembly for transcription factor access to genes is being assessed. Many groups are attempting to examine the influence of specific chromatin structures as determined in vivo on transcription in vitro. Finally the biochemical and genetic basis of long-range chromatin effects that appear responsible for position effect variegation are being explored. The purpose of this meeting is to bring together the most active groups in these overlapping research areas to discuss progress made, to identify questions of greatest current concern, and to discuss methodologies and techniques to be applied to these problem areas.

3. Organization

The purpose of the meeting is to bring together the most active researchers in this research area for the purpose of in-depth discussion, including the exchange of new and unpublished ideas and technology, in order to strengthen research efforts in the field. To accomplish this goal, the emphasis of the meeting will be on intensive but informal discussions of concepts, rather than long expositions of data. Data is to be presented, but only in support of ideas, not as an end in itself. Sessions will include 3-4 speakers, with each presentation lasting 40 minutes, followed by up to 20 minutes of discussion. This will give each speaker time to develop their conceptual line of thinking with supporting data, and provide adequate time for questions. There will be five morning sessions and four evening sessions. Afternoons will be left free for further discussion and informal associations. Poster sessions will be organized. Informal workshops on specific topics may be organized at the suggestion of meeting participants.

At this time the program is incomplete. This is intentional since the organizers (Alan Wolffe and Dan Gottschling) wish to select 4 to 6 additional speakers, but not until three to six months before the meeting. This is for three major reasons: 1) this research area is moving very quickly, new developments are certain to emerge in the next six months and we wish the meeting to be current; 2) we wish to encourage representation by female scientists and minorities, we will actively solicit further participation by such individuals during the next six months; 3) we wish to promote the work of scientists embarking on their professional careers, selection of speakers from this emerging group will be made once we receive applications to the meeting.

Enclosed are firm commitments from the 23 scientists named in this proposal (Appendix).

4. Program synopsis

The 1993 FASEB meeting on Chromatin and Transcription will feature nine sessions organized around the central theme of the meeting. The rationale, subject matter and principal speakers in these sessions are as follows:

MONDAY

1. Chromatin assembly
   Discussion leader: Dr. Mel De Pamphilis

The organization of the nucleosome and how it is assembled are central issues that provide a foundation for subsequent discussions concerning function. Dr. Van Moudrianakis (Johns Hopkins) has crystals of histone octamers in which the individual peptide backbones of the histones can be traced. An understanding of this and other nucleosome structures will be essential for subsequent discussion of the significance of histone-histone interactions and modifications. Dr. Bruce Stillman (CSH) will discuss the mechanism of chromatin assembly coupled to replication in the SV40 viral system. Dr. Fred Winston (Harvard) will describe proteins isolated through the application of yeast genetic screens that appear involved in chromatin assembly. Substantial progress should be described concerning how the gradual folding of DNA into chromatin is effected in vivo and in vitro.

2. Chromatin assembly and gene programming during development
   Discussion leader: Dr. Bruce Stillman

Chromatin structure is modified during the development of numerous organisms with severe functional consequences for gene activity. Drs. Mel DePamphilis (Roche), Dave Allis (Syracuse) and Alan Wolffe (NIH) will discuss how changes in histone modification and nucleosome structure influence the expression of genes in the developing mouse embryo, Tetrahymena and the frog embryo. How these chromatin modifications serve the purposes of the developing embryo or macronucleus and how they reflect modifications of the chromatin assembly process will be detailed and discussed.

TUESDAY

3. Chromatin structure of inducible genes
   Discussion leader: Dr. Carl Wu

One of the most powerful approaches to the study of chromatin and gene regulation involves systems in which specific alterations in chromatin structure can be induced by defined trans-activators. Particularly useful systems include those where these changes occur in the absence of complicating issues such as DNA replication. A discussion of these systems will include contributions from Dr. Wolfram Horz (Munich) (PHO5 induction in yeast) and Dr. Gordon Hager (NIH) (glucocorticoid induction of MMTV).

4. Roles of nucleosomal structure in gene regulation
   Discussion leader: Dr. Roger Kornberg

The organization of eukaryotic promoters into specific chromatin structures has important consequences for the transcription process. Two leading experts: Dr. Carl Wu (NIH) and Dr. Jim Kadonaga (San Diego) in in vitro transcription have applied their expertise to examine the implications of nucleosome formation for the transcription initiation process.

WESNESDAY

5. The influence of transcription factors on nucleosomal organization
Discussion leader: Dr. Bruce Alberts

An increasing body of work demonstrates that transcription factors can exert direct effects on the positioning of nucleosomes. Dr. Bob Simpson (NIH) has evidence suggesting contacts between the yeast homeodomain protein $\alpha 2$ and the amino terminus of yeast histone H4, these contacts lead to specific nucleosome placement over the promoters of genes repressed by $\alpha 2$. Dr. Roger Kornberg (Stanford), who has studied this problem for over a decade will also contribute to this discussion of nucleosome positioning. Dr. Michael Grunstein has pioneered the influence of directed histone mutation on gene expression in yeast and will discuss the latest results concerning the influence of the histone tails on nucleosome placement and transcription.

6. The chromatin fibre and transcription
Discussion leader: Dr. Sally Elgin

The next level of organization in chromatin above the nucleosome is the formation of the chromatin fibre. The folding of nucleosomal arrays has important consequences for both transcription initiation and the elongation of RNA polymerases. Dr. Jean Thomas (Cambridge) will discuss the consequences for transcription of variation in the histones that direct the folding of nucleosomal arrays. Drs. Ken van Holde (Oregon) and Morton Bradbury (Davis) will discuss the implications and consequences of chromatin folding for the progression of RNA polymerase through arrays of nucleosomes, in either extended or folded configurations.

THURSDAY

7. Chromosomal domains and gene regulation I
Discussion leader: Dr. Wolfram Horz

Drs. Jasper Rine (Berkeley) and Amar Klar (Frederick) will discuss recent genetic evidence concerning long range effects on gene expression, particularly those impacting on expression of the mating type loci in yeast. Possible models involving both chromatin modification and nuclear architecture will be detailed.

GRADUATE STUDENT/POST DOCTORAL FELLOW TRAVEL AWARDS (2) - 10 min presentation.

8. Chromosomal domains and gene regulation II
Discussion leader: Dr. Jasper Rine

Dr. Adrian Bird (Edinburgh) has made substantial progress in defining mechanisms whereby eukaryotic DNA methylation might influence chromatin structure and hence gene expression.

Dr. Dan Gottschling (Chicago) has uncovered position effect variegation in yeast and embarked on a genetic analysis of this problem. The experimental results from both of these speakers will extend the discussion of chromosomal domains beyond mating type to other regions of the yeast chromosome and to large eukaryotes.

9. Heterochromatin and the global control of gene expression
Discussion leader: Dr. Jean Thomas

Rapid progress has recently been made in defining a new family of chromatin binding proteins containing the 'chromodomain', for example: the Drosophila proteins polycomb and HP1. The latest results in this field will be discussed by three leading workers: Drs. Sally Elgin (Washington Univ., St. Louis), Dr. Barbara Wakimoto (Univ. Washington, Seattle) and Dr. Bruce Alberts (UCSF).

5. Other activities

Graduate Student/Postdoctoral Fellow Travel Award

In the atmosphere of restricted research funding it is often difficult for many laboratories to adequately support the travel costs for trainee personnel, such as students and postdoctoral fellows, who may be just embarking on research career in protein phosphatases. Clearly such an intense "course" as that provided by the FASEB Summer Conference with the opportunity to interact with and discuss their work with more experienced scientists is enormously beneficial to such junior investigators. To encourage their involvement in this conference, the committee has recommended the institution of a travel award for graduate students/postdoctoral fellows. Only two such awards are currently budgeted in our calculations (see below). Abstracts submitted by the applicants will be reviewed by the organizers and the selection of awardees will made on the grounds of the novelty of the research and the qualifications of the applicants. Letters of recommendation emphasizing the contributions of the graduate student/postdoctoral fellow to the project may be sought at the request of the committee. The winners will be given the opportunity to present their work in the form of an oral presentations in the program.

6. Other meetings

Only one current meeting addresses this general area in five of its nine sessions: the biannual Gordon Conference on Nuclear Proteins held at Tilton, New Hampshire. This meeting will be held in Summer 1992, and will not occur again until Summer 1994. This meeting is very highly regarded, is always oversubscribed in its attendance (> 400 applicants for 150 places), and is a great success. This meeting, however covers the complete range of topics related to nuclear structure, including biophysical characterization of chromatin and its various component structures, chromosome and nuclear organization, nuclear matrix, scaffold and skeleton, domain structure, replication, recombination and transcription. The subject matter is too broad to effectively focus on the topic of the FASEB meeting (i.e. how does chromatin structure impact on transcription?) Most importantly the momentum of scientific research in this specific area is developing much too rapidly to be considered only once every two years. A forum is needed in which the very complex issues presented by this subject matter can be addressed over an extended period of time by those biologists who are most active in this area. The FASEB meeting will provide this forum.